Psychosocial and pharmacological treatments for cannabis use disorder and mental health comorbidities: a narrative review

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Abstract

Cannabis is the most widely used illicit drug worldwide, and it is estimated that up to 30% of people who use cannabis will develop a Cannabis Use Disorder (CUD). Treatment demand for CUD is increasing in almost every world region and cannabis use is highly comorbid with mental disorders, where sustained use can reduce treatment compliance and increase risk of relapse. In this narrative review, we outline evidence for psychosocial and pharmacological treatment strategies for CUD, both alone and when comorbid with psychosis, anxiety or depression. Psychosocial treatments such as CBT, MET and contingency management are currently the most effective strategy for treating CUD but are of limited benefit when comorbid with psychosis. Pharmacological treatments targeting the endocannabinoid system have the potential to reduce cannabis withdrawal and cannabis use in CUD. Mental health comorbidities including anxiety, depression and psychosis hinder effective treatment and should be addressed in treatment provision and clinical decision making to reduce the global burden of CUDs. Antipsychotic medication may decrease cannabis use and cannabis craving as well as psychotic symptoms in patients with CUD and psychosis. Targeted treatment for anxiety and depression when comorbid with CUD are feasible.

Introduction

Cannabis is the most commonly used illicit drug globally. It is estimated that approximately 3.8% of the global population (188 million people) aged 15-64 used cannabis in the last year (UNODC, 2019). Cannabis use is especially prevalent in adolescents and young adults, with 18% of European 15-24 year olds, compared to 7.4% of 25-64 year olds having tried cannabis in the past year (European Monitoring Centre for Drugs and Drug Addiction, 2019). Many people who use cannabis do so infrequently, and without major problems. However, epidemiological studies suggest that approximately 3 in 10 users go on to develop a problematic pattern of use characterised by continued use despite persistent adverse consequences (Hasin *et al.*, 2015; Marel *et al.*, 2019). Cannabis Use Disorder (CUD) refers to recurrent use of cannabis despite negative impact on the individual's life, causing clinically significant impairment or distress (American Psychiatric Association, 2013). CUD replaced earlier diagnostic criteria of problematic use represented in DSM-IV-TR as separate diagnoses

for “Cannabis abuse” and “Cannabis dependence” which remain widely used in the literature at present.

New medical and recreational cannabis laws, as well as increased discourse about cannabis and cannabinoids as medical products, have the potential to influence public perceptions of cannabis including the risks associated with its use. This could influence access to cannabis, as well as acceptability of treatment. However, despite public perception of the harmfulness of using cannabis decreasing over recent years (Hasin, 2018), the role of changing cannabis laws in this trend is unclear, (Keyes *et al.*, 2016) and the impact this may have on treatment demand is also uncertain (Budney *et al.*, 2019).

Accumulating evidence suggests that CUDs are common and they often go untreated (Khan *et al.*, 2013; Hasin *et al.*, 2016; Kerridge *et al.*, 2017). It is estimated that there are 22 million people worldwide with a cannabis use disorder (CUD), comparable to an estimated 27 million for opioid use disorders (Degenhardt *et al.*, 2018), highlighting a clear clinical need for effective treatments. Regular cannabis use is associated with various negative mental health outcomes such as psychosis, anxiety and depression (Patton *et al.*, 2002; Leadbeater *et al.*, 2019). Comorbidity between problematic cannabis use and other mental health disorders can create significant challenges for patients and treatment providers.

In this narrative review, we discuss state-of-the-art clinical evidence on the treatment of CUDs. We begin by reviewing the latest evidence for psychosocial and pharmacological treatments. Next, we discuss treatments targeting CUDs comorbid with psychosis. This is a particularly important treatment need, given cannabis is used by an estimated 33.7% of people with first-episode psychosis (Myles *et al.*, 2016) and continued cannabis use is consistently associated with poorer clinical outcomes including longer hospital admissions, more severe positive symptoms (Schoeler *et al.*, 2016) and poor medication adherence leading to relapse (Schoeler *et al.*, 2017). Finally, we focus on treatments targeting CUD when comorbid with anxiety and depression. Anxiety and depression are common mental disorders, are highly comorbid with CUD (Hasin *et al.*, 2016) and can influence treatment outcomes. For example, anxiety is associated with greater withdrawal symptom severity from cannabis use (Buckner *et al.*, 2017) and depression is associated with lower likelihood of cannabis abstinence during a cessation attempt (Tomko *et al.*, 2020).

Search Strategy and Selection Criteria

Articles for this review were obtained from searching PubMed, PsychInfo, Google Scholar, Embase and Medline databases and the Cochrane Review database for key terms “Cannabis” “THC” “CUD” “Cannabis use disorder” “Psychosis” “Anxiety” “Depression” “Treatment” “Dual Diagnosis” from inception up to 24/02/2020. Additional articles were obtained from reference lists of existing papers and reviews. We searched the relevant grey literature (UNODC, EMCDDA) for the most up to date information on CUD internationally. RL ran the literature searches and consulted all authors on the inclusion of studies. We included studies that investigated psychosocial or pharmacological treatment options for CUD, including samples with and without comorbidities. Most of the included studies were randomized control trials (RCTs), although other experimental designs were included where RCTs had not been conducted or were inconclusive. Studies with both inpatient and outpatient designs were eligible. Trials were prioritized for inclusion based on methodology (such as large multisite RCTs) and novelty to the field. Where several trials of the same intervention had been conducted with converging results, we discuss the key trials. Studies predominantly used DSM-IV criteria, although studies that measured CUD in other ways (ICD, CUDIT, DSM-5) were included.

Treatment of Cannabis Use Disorders

Treatment demand for cannabis use is increasing globally in every region except Africa (UNODC, 2019). In Europe, 155,000 individuals entered treatment for problems related to cannabis in 2017, with over half entering treatment for the first time (Montanari *et al.*, 2017; European Monitoring Centre for Drugs and Drug Addiction, 2019). A possible contributor to these changes is the increase in cannabis potency in recent decades (Freeman *et al.*, 2020a) which has been associated with elevated treatment admissions for CUDs (Freeman *et al.*, 2018). In fact, cannabis is now responsible for more first time admissions than any other drug in Europe (Figure 1; European Monitoring Centre for Drugs and Drug Addiction, 2019). A typical client entering drug treatment for cannabis initiates use at age 17, enters treatment at 25, and uses cannabis 5.3 days per week at treatment entry.

Whilst these treatment data are indicative of the extent of problematic use in the population, prevalence of CUD is much greater and it is estimated that over 85% of individuals with lifetime CUD do not seek treatment (Hasin *et al.*, 2016). In Europe, there is considerable

variation by country in estimates of unmet cannabis treatment needs. While treatment provision is high in some countries (e.g. Germany, Norway) where one in ten daily users receive treatment, it is low in others (including Italy, Spain and France) where one to three of every 100 daily users receive treatment (Schettino *et al.*, 2015). In a large survey of adults with CUD in the US, 10.28% had received drug treatment of any kind in the past year, with only 7.81% having received cannabis-specific treatment (Wu *et al.*, 2017).

Psychosocial treatments (Table 1)

There is good evidence that psychosocial treatments can be effective for the treatment of cannabis use disorders. Treatment options are often not developed specifically for use in CUD and many have been adapted from existing substance use treatments (Schettino *et al.*, 2015). Cognitive Behavioural Therapy (CBT) and Motivational Enhancement Therapy (MET) can reduce frequency and intensity of cannabis use as well as symptoms of dependence, in comparison to inactive control, and can be delivered in combination (Gates *et al.*, 2016). For example, an RCT of 10-week combined CBT, MET and problem solving training treatment (n=149) compared to delayed treatment control (n=130) was conducted at 11 outpatient treatment centres in Germany (Hoch *et al.*, 2014). Compared to control, treatment improved rates of self-reported abstinence and urinary-verified abstinence at post-treatment, though reported abstinence rates decreased at 6-month follow-up in the treatment group. Treatment also impacted the number of ICD-10 cannabis dependence criteria met at post-treatment, however rates of dependence or abuse were low in the sample at baseline (56.3 and 8.6%, respectively).

Psychotherapies are appropriate in adolescent samples, and inclusion of the patient's family in treatment may be particularly effective. For example, an international multi-site RCT (Rigter *et al.*, 2013) found that a 6 month programme of Multidimensional Family Therapy (n=212) reduced cannabis dependence in adolescents better than individual psychotherapy (n=238) over the same time period, with a significantly greater shift from dependence to abuse or no CUD in the family therapy group.

Brief versions of MET have also been investigated, primarily in school based settings, to ascertain whether psychosocial treatment can be employed without lengthy and intensive treatment intervention (Walker *et al.*, 2011). In one such RCT from the USA, adolescents received 2 sessions of MET, and were then randomly assigned to a motivational check in

(n=128) or assessment- only check in (n=124), with extra CBT sessions offered but not enforced (Walker *et al.*, 2016). The two sessions of MET reduced cannabis use in both conditions, with the motivation check-in group showing a larger reduction in days of use and fewer symptoms at 6-months, however this was not sustained at 9- or 12- month follow up.

Evidence suggests that adding contingency management (CM) of monetary incentives for abstinence outcomes to combined CBT + MET can increase the likelihood of reducing cannabis frequency and achieving abstinence into longer term follow ups (Kadden *et al.*, 2007). In fact, evidence from RCTs in the USA suggests that CM alone can reduce cannabis use more effectively than CBT during the treatment period. For example, (Budney *et al.*, 2006) found the average number of weeks of continuous abstinence during treatment were significantly superior in a CM-only condition (n=30) than CBT (n=30), and adding CBT to CM did not offer any additional benefit (n=30). However, the analysis of continuous abstinence was underpowered and therefore potentially important differences between groups may not have been detected. This was mirrored in findings by (Kadden *et al.*, 2007) who found a CM-only condition to have superior rates of abstinence at post-treatment to MET-CBT in a large (n=240), 9-week RCT from the US, though abstinence rates then declined after 5 months. Combined MET-CBT and CM yielded the longest periods of continuous abstinence during the follow-up year and resulted in the greatest proportion of individuals abstinent at 11- and 14-month follow-up.

Finally, there is evidence of small treatment effects for digital interventions on reducing cannabis use (Hoch *et al.*, 2016). The most promising results come from an RCT conducted in Germany (Tossmann *et al.*, 2011) that employed online discussion with a trained psychotherapist, including weekly personalised feedback based on CBT (n=863), compared to waiting list (n=429). The treatment group showed a greater reduction in days of use over the last 30 days compared to waiting list as well as reduced quantity of cannabis used at follow-up conducted 3-months after enrolment on the programme. However, these analyses were not sufficiently powered due to low engagement and high dropout rates. Preliminary evidence from an RCT conducted in the USA showed that a 4-week text-delivered treatment reduced the proportion of the sample reporting cannabis-related relationship problems (n=51) significantly more than an assessment-only control (n=50). However, there was no reduction in frequency of cannabis use (Mason *et al.*, 2018). Further, retention was high with 96% of participants completing 3-month follow-up. Digital interventions so far have produced mixed findings, but

given their potential for tackling barriers to treatment engagement, larger trials assessing their reduction in cannabis use as well as diversity of population they can reach are warranted. Further digital interventions such as smartphone apps show promise in this area (Albertella *et al.*, 2019) and have the potential to reach the substantial number of people who do not seek in person treatment for CUDs at present.

Pharmacological treatments (Table 2)

A 2019 Cochrane review concluded that there were no high-quality indications of an effective pharmacological treatment for CUD based on available evidence (Nielsen *et al.*, 2019). Since the publication of this review there have been several new trials of pharmacological treatment of CUDs (D'Souza *et al.*, 2019; Lintzeris *et al.*, 2019; Freeman *et al.*, 2020b). Moreover, the Cochrane review based its recommendations on abstinence achieved at the end of treatment. However, expert consensus recommends that sustained abstinence should not be considered the primary outcome for all clinical trials of CUD (Loflin *et al.*, 2020).

Substitution cannabinoid treatments

Several studies have investigated the effects of Dronabinol (synthetic THC) or Nabiximols (THC and CBD at 1:1 ratio) for the treatment of CUD and/or cannabis withdrawal. An RCT conducted in the USA (Levin *et al.*, 2011) found that 40mg daily Dronabinol (Treatment n=70, Placebo n=77) in combination with MET was superior to placebo at reducing severity of withdrawal symptoms but not rates of 2-week abstinence. Days of cannabis use measured via an extensive TLFB method was also not significantly different between Dronabinol and Placebo. Additionally, a 2-site inpatient detoxification trial in Australia (Allsop *et al.*, 2014; Treatment n=27, Placebo n=24) of six days Nabiximols combined with MET/CBT was found to reduce withdrawal, and improve treatment retention, but was not associated with greater reduction in cannabis use. Further a pilot, outpatient RCT in Canada (Trigo *et al.*, 2018) found no significant difference in frequency of cannabis use or withdrawal symptoms for 12-week treatment of flexible Nabiximols use combined with weekly MET/CBT (n=20) compared to MET/CBT alone (n=20). The Nabiximols group reduced their tobacco use over the trial. A multi-site, outpatient RCT conducted in Australia (Lintzeris *et al.*, 2019) tested 12-week flexible Nabiximols treatment with 6 sessions of CBT (n=64) compared to placebo and 6 sessions of CBT (n=73). Contrasting with previous findings, Nabiximols reduced frequency of cannabis use during the trial compared to placebo but did not significantly reduce cannabis withdrawal over placebo. These results were sustained at 12-week follow-up (Lintzeris *et al.*,

2020). This study monitored nicotine and alcohol dependence over the treatment period and found no change over time or any group differences. Overall, evidence suggests that substitution treatments containing THC typically reduce withdrawal symptoms but evidence for their effectiveness at reducing cannabis use is mixed and may depend on the setting and duration of treatment.

Non-substitution cannabinoid treatments

Trials have also tested alternative pharmacological treatments acting on the endocannabinoid system (Parsons and Hurd, 2015). A Phase II RCT involving 5 day enforced-abstinence followed by four-week treatment with the FAAH inhibitor PF-04457845 (n=46; D'Souza *et al.*, 2019) compared to placebo (n=24) found reductions in self-reported use of cannabis at the end of treatment, and THC:COOH concentrations, as well as reduced cannabis withdrawal symptoms on the first and second day of enforced abstinence. As PF-04457845 did not have sufficient safety data in females at the time of this study, only male participants were included. These safety data are now available, and a subsequent Phase III trial (n=273) including males and females is currently underway. Finally, a Phase IIa adaptive Bayesian RCT conducted in the UK (Freeman *et al.*, 2020b) tested CBD at daily doses of 200mg, 400mg, 800mg versus placebo for four weeks alongside six sessions of motivational interviewing. CBD was more efficacious than placebo at reducing cannabis at daily doses of 400mg or 800mg (posterior probabilities > 0.9) but not 200mg (posterior probability <0.1). Cannabis use measured via self-report and urinary THC:COOH was reduced compared to placebo (n=23) following 400mg (n=24) and 800mg (n=23) CBD. Reductions in cannabis use were maintained up to 24-week follow up with 400mg CBD but not 800mg CBD. These results suggest a possible inverted-U dose-response curve effect of CBD on cannabis use, consistent with CBD effects on anxiety (Zuardi *et al.*, 2017). Longer follow-ups and RCTs specifically designed to determine efficacy are required to extend these results. Both FAAH inhibitors and CBD can increase concentrations of the endocannabinoid anandamide (Leweke *et al.*, 2012; D'Souza *et al.*, 2019). These non-substitution cannabinoid treatments offer possible strategies to treat CUDs through endocannabinoid system mechanisms, without risk of harm from THC administration.

Other pharmacological treatments

An RCT from the USA investigating N-acetylcysteine added on to contingency management treatment has shown effectiveness at treating CUD in adolescents (Gray *et al.*, 2012). Those receiving N-acetylcysteine treatment (n=58) were 2.4 times more likely to submit a negative

urinary screen for cannabis use compared to placebo (n=58). There was no significant difference in change of days with self-reported cannabis use across the trial between groups. Contrasting results were found in a subsequent multi-site RCT of adults with CUD (Gray *et al.*, 2017) where negative urinary screens were not statistically different between N-acetylcysteine (n= 153) and placebo (n=149). These treatment effects were not moderated by sex, ethnicity or tobacco smoking status. However, baseline tobacco use was a significant predictor of negative cannabis outcomes in general, with tobacco smokers half as likely to achieve abstinence from cannabis in both groups. These findings illustrate the importance of considering tobacco use in the treatment of CUD.

There is some evidence for the effectiveness of gabapentin in the treatment of CUD from an RCT in the USA (Mason *et al.*, 2012). Gabapentin together with abstinence-oriented counselling demonstrated superiority at 1200mg/day for 12 weeks (n=25) over placebo (n=25), at reducing cannabis use as verified through reduced self-reported grams of cannabis, fewer self-reported days of cannabis use and reduced urinary THC-COOH concentrations as well as lower cannabis withdrawal severity. However, a limitation was high levels of drop out in the trial (n=18 for Gabapentin; n=14 for placebo). Moreover, a larger trial (Mason, 2017) of Gabapentin 1200mg/day for 12 weeks (n=75) did not demonstrate efficacy compared to placebo (n=75).

In summary, substitution cannabinoid treatments containing THC appear effective at reducing cannabis withdrawal but evidence has been mixed for changes in cannabis use. Other treatments targeting the endocannabinoid system (FAAH inhibition and CBD) and N-acetylcysteine (in adolescent, but not adults) show proof of concept evidence for reducing cannabis use, but require replication in larger trials.

Psychosis (Table 3)

A Cochrane review published in 2014 concluded that there is a lack of good quality evidence for the efficacy of any psychosocial or pharmacological treatment at reducing cannabis use in psychosis (McLoughlin *et al.*, 2014). Studies conducted since the publication of that review have had mixed findings (Smeerdijk *et al.*, 2012; Rabin *et al.*, 2018; Sheridan Rains *et al.*, 2019). Tailored and time-intensive cannabis-focused treatment plans have not provided better outcomes than treatment as usual (Wisdom *et al.*, 2011). For example, a superiority trial

conducted in Denmark using weekly motivational interviewing and CBT targeted specifically at patients with psychosis who continued to use cannabis (n=52), found similar reductions in cannabis use at the end of treatment and follow up as treatment as usual (n=51), targeted only towards psychotic disorder (Hjorthoj *et al.*, 2013).

A small feasibility study of Canadian males found that supportive therapy alongside a $300 payment for 28 day abstinence was associated with 68.4% of patients with CUD and schizophrenia (n=19), reporting abstinence, compared to 95% of patients with CUD-only (n=20) reporting abstinence. However, negative urinary screens were only present in 47.3% of patients with schizophrenia, and 40% in CUD-only (Rabin *et al.*, 2018). Replication of these findings has not been achieved in subsequent RCTs to date. A large (n=551, treatment n=278), multi-centre RCT from the UK (Sheridan Rains *et al.*, 2019) investigating the addition of a voucher-incentive programme to early intervention psychosis treatment did not find a difference in the primary outcome of time to admission to an acute mental health service, and no difference on self-reported cannabis use at the end of treatment.

Finally, a trial conducted in the Netherlands demonstrated that a family motivational intervention (Parents n=53, Patients n=37) which focuses on establishing a supportive family environment, compared to routine family support (Parents n=44, Patients n =38) was effective at reducing frequency and quantity of cannabis use in adolescent and young adult patients with schizophrenia at 3 month follow-up (Smeerdijk *et al.*, 2012). This was sustained at 15-month follow-up (Smeerdijk *et al.*, 2015). There were no significant changes from baseline in use of alcohol or any other drugs other than cannabis during this trial.

Overall, RCT data suggests that psychosocial treatments that appear effective in CUD-only patients (including contingency management) do not appear effective for patients with comorbid psychosis. However, involvement of the family in treatment appears successful in some patients and is a possible strategy for future research. In addition to psychosocial treatments, the effects of digital interventions are currently unclear, but a targeted, self-guided web-based programme is currently being trialled for young people with psychotic experiences and cannabis use in Australia (Hides *et al.*, 2020).

Evidence for the role of pharmacological treatments for CUDs in people with psychosis is lacking at present. A systematic review found preliminary evidence that some antipsychotic

medications might be effective at reducing both cannabis use and psychotic symptoms (Wilson and Bhattacharyya, 2015). Both clozapine (n=14) and ziprasidone (n=16) were associated with significant reduction in cannabis use and psychotic symptoms (PANSS positive), in a pilot study conducted in Germany (Schnell et al., 2014). Further evidence from (Machielsen *et al.*, 2011) suggests that olanzapine treatment (n=52) is associated with lower cannabis craving in comparison to risperidone (n=48) in patients with psychotic disorder and cannabis dependence as measured using the craving subscale of the Obsessive Compulsive Drug Use Scale. However, this comparison used cross-sectional data from a larger study conducted in the Netherlands rather than an RCT design. Altogether, evidence suggests that standard antipsychotic treatment for psychosis may have additional benefits for patients with comorbid CUD. Future research should consider whether any additional treatment options are efficacious to further support these patients. Further, other pharmacological treatments that have been investigated in CUD have not been explored in comorbid psychosis, so their efficacy in these patients is unknown at present.

Pharmacological management of CUD and psychosis should consider interactions between cannabis and prescribed antipsychotic medication (Brzozowska *et al.*, 2017). Such drug-drug interactions may account for poor antipsychotic medication adherence, which mediated the effects of cannabis use on relapse to psychosis in a two-year prospective observational study (Schoeler *et al.*, 2017). Emerging evidence strongly implicates the endocannabinoid system in psychosis (Minichino *et al.*, 2019) as well as addiction (Curran *et al.*, 2016) which presents a promising target for future treatments. Antipsychotic treatments which act on the endocannabinoid system (CBD) have produced favourable outcomes (Leweke *et al.*, 2012; McGuire *et al.*, 2017). One possible strategy is CBD for the treatment of comorbid CUD and psychosis (Batalla *et al.*, 2019). Due to the poor efficacy of psychosocial interventions for comorbid CUD and psychosis, and the poor clinical outcomes associated with continued cannabis use in this population, the development of effective pharmacological treatments is an urgent priority.

Anxiety and depression (Table 4)

A large multisite RCT in the USA (Buckner and Carroll, 2010) reported that 9 sessions of CBT tailored to CUD (n=156) compared to 2-session MET alone (n=146) reduced anxiety and that reduction was correlated with successful reduction in CUD. Further, a small pilot trial

conducted in the USA combining cannabis-tailored MET-CBT with transdiagnostic anxiety treatment (ICART, n =27) showed preliminary evidence of increased rates of abstinence at the end of treatment over MET-CBT alone as confirmed using urinalysis. Targeted treatments for depression have also been investigated. For example, a study from Australia (Kay-Lambkin *et al.*, 2009) found that motivational interviewing plus CBT treatment tailored for both depressive symptoms and comorbid cannabis use (SHADE, n=67) resulted in significant overall reductions in cannabis use over 12 months, and reductions in depressive symptoms compared to a brief intervention (n=97). There is no current evidence for an effective pharmacological treatment for both depression and CUD. SSRIs have been investigated as a treatment for CUD, and have not proven efficacious (Weinstein *et al.*, 2014; McRae-Clark *et al.*, 2016). Moreover, trials investigating fluoxetine and venlafaxine specifically for comorbid depression and CUD, have not found improvement in CUD or depression in comparison to placebo (Cornelius *et al.*, 2010; Levin *et al.*, 2013).

Taken together, it appears feasible to target comorbid CUD with anxiety or depression effectively with psychosocial treatment and this should be encouraged. To date, pharmacological treatments specifically targeting CUD comorbid with anxiety or depression have not been successful.

Summary of findings and critical appraisal

Current evidence suggests that psychosocial treatments including CBT, MET and CM can increase duration of abstinence from cannabis, reduce frequency of cannabis use, and reduce symptoms of CUD, and their combination may yield most effective results over the long-term. Trials of psychosocial interventions benefit from large sample sizes and multi-site designs, which increase power and generalisability. Of note, clinical trials of psychosocial interventions typically employ waiting list or low-intensity treatments as a control intervention. This could artificially inflate the effect sizes observed in such trials (Furukawa *et al.*, 2014) due to a lack of expectancy from a matched placebo, alongside negative effects of psychosocial control conditions ("nocebo" effects), and this should be considered when interpreting findings across different trial designs.

Psychosocial treatment interventions are generally associated with positive during-treatment effects, though these attenuate at follow-up and long-term clinical efficacy needs to be assessed with longer follow-up periods. Most interventions encourage complete abstinence from

cannabis use, but are flexible towards individual goals. Sustained abstinence does not occur for the majority of patients. Further evidence is required to compare the efficacy of emerging digital interventions to in-person treatment, and to address the high dropout level observed in online interventions. Research is required to assess whether digital interventions could tackle some of the key barriers to treatment seeking in CUD including stigma and desire for more informal treatment options.

Several trials have investigated substitution treatments (medications containing THC) to treat CUD or aid in detoxification from cannabis. Generally, these trials observe high rates of reduction of cannabis in both treatment and placebo groups, likely due to a beneficial effect of the paired psychotherapies typically employed in experimental and control conditions in these trials. This should be considered when comparing the efficacy of pharmacological treatments with psychosocial treatments, as pharmacological treatments are tested as adjunctive therapies which may limit their potential to provide additional benefits to an effective psychosocial intervention. Additionally, based on the current evidence it is not clear whether psychosocial treatments are necessary in order to promote retention in CUD trials or to facilitate the efficacy of pharmacotherapies. Future trials should aim to investigate the additive or synergistic effects of psychosocial and pharmacological treatments in order to maximise efficacy and cost-effectiveness. Moreover, pharmacological trials are often based on small sample sizes with shorter follow-up periods, a reflection of their currently early phase of assessment.

Despite this, treatments are associated with increased retention as well as reduction in withdrawal symptoms, though lack of longer-term follow-ups creates difficulty in assessing whether the beneficial impact on reducing withdrawal symptoms translates to meaningful clinical outcome in the long-term. Other pharmacological treatment strategies targeting the endocannabinoid system including CBD and FAAH inhibition show promise, but require replication in larger RCTs with longer follow-up durations.

An important consideration when evaluating findings across trials is that treatment outcome is defined in many different ways. Typically, likelihood or duration of abstinence is included as a primary indicator of treatment success. However, reductions in frequency and quantity of use also mark a positive treatment response, especially when biological measures such as urinalysis are employed to quantify use (Loflin *et al.*, 2020). For shorter-term interventions, reduction in

cannabis craving or withdrawal may represent positive treatment response in the absence of reduction in cannabis use.

Further, the majority of trials discussed in this review were conducted in samples of >70% male participants. Consequently, the impact of sex on treatment outcomes in CUD is unclear. This is important as women experience more rapid escalation of problems from first use to CUD than men, even when matched for age at first or heavy use (Khan *et al.*, 2013; Crocker and Tibbo, 2018). Women also experience more withdrawal symptoms and greater withdrawal severity than men (Herrmann *et al.*, 2015). Increasing female participants in RCTs for CUD treatment, as well as investigating sex as an *a priori* moderator of treatment efficacy and safety is needed to establish sex-specific treatment recommendations for clinical practice. Further, mental health comorbidities are frequently used as exclusion criteria, which means these samples are likely not representative of the wider population of people with CUD who might respond differently to treatment. Similarly, most trials exclude participants with another substance use disorder (SUD), other than nicotine and caffeine. Where such comorbidities are not an exclusion criterion, they are often not assessed throughout the treatment period and subsequently their impact on treatment outcome is not explored. SUDs commonly overlap with CUD, and also with other mental health disorders (Hasin *et al.*, 2016). Comorbid SUDs can also impact on treatment need and efficacy. For example co-occurring cannabis and tobacco use is associated with increased likelihood of developing CUD, as well as poorer cessation treatment outcomes including relapse to cannabis use (McClure *et al.*, 2020). Ascertaining the impact of comorbidities on efficacy of treatment for CUD is vital to be able to personalise treatment options depending on the patient's mental health and substance use profile.

Taken together, our recommendations for future interventions for CUD are to ensure that studies are sufficiently powered, in particular by considering recruiting sufficiently large sample sizes to deal with dropout observed in interventions for CUD. Further, researchers should consider whether findings replicate in populations with CUD and mental health comorbidities. Trials should ensure that follow-ups have been planned with sufficient duration to assess whether treatment effects persist following treatment completion. Finally, primary endpoints assessing sustained reduction in cannabis use should be employed alongside, or instead of, measuring sustained abstinence.

Another consideration for future research is the large proportion of individuals not seeking out or accessing treatment who may benefit from it. Among non-treatment seeking users with cannabis dependence, lack of motivation (not believing anyone could help the problem, wanting to handle the problem alone) has been found to be a major contributor to not seeking treatment (Khan *et al.*, 2013). Stigma also appears as a common barrier to treatment, with individuals reporting feeling embarrassed about seeking treatment. Desire to be self-reliant as well as preference for informal treatment options has also been identified in non-treatment seeking users with cannabis dependence (van der Pol *et al.*, 2013) which may indicate advantages of digital interventions compared to more intensive treatment programmes. Further, improving the information available about treatment services as well as simplifying treatment admission processes have been identified as perceived facilitators of treatment (Gates *et al.*, 2012). Finally, access and affordability of drug treatment options could create a significant barrier to treatment engagement, particularly in countries such as the US. Therefore, increasing access, acceptability and perhaps variety of treatments is an important goal for alleviating the adverse effects of untreated CUDs. These factors may also relate to individuals' willingness to take part in clinical trials of interventions for CUD, and may partially explain high rates of dropout suffered in such trials e.g. (Mason *et al.*, 2012). Future research should work directly with individuals seeking treatment for CUD, to expand our understanding of the acceptability of current treatment options as well as exploring which factors facilitate treatment seeking.

Finally, this review highlights the particular challenges of treating CUD in people with mental health comorbidities. For example, contingency management appears effective in those with CUD, however trials have not replicated this effect in those with comorbid psychosis. Most pharmacological interventions have not been explored in people with mental health comorbidities. The lack of efficacious treatments in this population highlights a major unmet clinical need at present. Antipsychotic medication also could play an important role in the management of comorbid CUD and psychosis, with some medications such as clozapine and olanzapine associated with a reduction in cannabis craving. Psychosocial treatments targeting dual diagnosis appear beneficial for management of CUD with anxiety and depression. While mental health comorbidities are common in people with CUD, evidence on the efficacy of treatments in this population is extremely limited and should be addressed as a research priority.

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Table 1. Study design and primary endpoint data for psychosocial interventions for CUD

Study	Interventions	Primary endpoint(s)
Hoch et al., 2014	CBT + MET + Problem solving (n= 255), 10-week Delayed treatment control (n= 130), 8-week	CBT + MET+ problem solving intervention increased rates of urinary-verified 7-day abstinence from baseline to end of treatment (11.7% - 46.3%), a greater increase than the delayed treatment control (9.3% - 17.7%), p<.001. Urinary-verified 7-day abstinence rates in the CBT + MET + problem solving group were 32.4% at 3 months, and 35.7% at 6 months. Urinary-verified abstinence rates for delayed treatment control at 3 and 6 months not provided as they had entered treatment.
Rigter et al., 2013	Multidimensional family therapy (n= 212), 6-month Individual psychotherapy (n= 238), 6-month	Multidimensional family therapy increased retention in treatment (90% therapist-reported completion) compared to individual psychotherapy (48% therapist-reported completion), p<.001. Multidimensional family therapy reduced prevalence of diagnosis of either cannabis abuse or dependence from baseline to 12-month follow-up (100% - 71%), a non-significant change compared to individual psychotherapy (100% - 74%). Multidimensional family therapy reduced past-90 day cannabis use from baseline to 12-month follow-up [59.8(25.3) – 34.0(32.6)] a non- significant decrease compared to individual psychotherapy [61.25(25.4) – 42.3(33.8)].
Walker et al., 2016	2 session brief MET + motivational check-in (4-, 7-, 10-month) (n=128) 2 session brief-MET + assessment only check-in (4-, 7-, 10- month) (n= 124)	Motivational check-in intervention reduced past-60 day use from baseline to 6-month [36.80(15.16) – 26.64(20.25)], a greater reduction in use than the assessment-only check-in intervention [37.35(15.01) – 32.66(19.91)], p=.01.
Budney et al., 2006	CBT (n= 30), 14-week	Contingency Management produced significantly greater weeks of continuous abstinence during treatment than CBT [6.9(5.4) vs 3.5(3.2)], p<.05. Adding CBT to Contingency

	Contingency Management (n= 30), 14-week CBT+ Contingency Management (n= 30), 14-week	Management did not produce a significant difference in continuous abstinence [5.3(4.7)] compared to Contingency Management alone. Contingency management alone, and combined with CBT yielded a greater percentage of patients achieving 6 or more weeks of abstinence during treatment than CBT alone (Contingency management = 50%, Contingency management + CBT = 40%, CBT = 17%), p<.05.
Kadden et al., 2007	CBT + MET (n= 61), 9-week CBT + MET + CM (n= 63), 9-week CM (n= 54), 9-week Case Management (n= 62), 9-week	Treatment interventions did not significantly differ in achieved proportion of days abstinent at 2-month or further follow-ups. Contingency management produced a significantly greater proportion of days abstinent at 2 month, compared only to case management (p<.05).
Tossman et al., 2011	Web-based treatment (n= 863), 50-day Waiting List (n= 429), up to 3 months	Web-based treatment produced a greater reduction in last-30 day frequency of cannabis use from baseline to 3-month follow up [25.1(6.9) – 16.5(20.9)] compared to waiting list [25.3(6.5) – 21.0(17.1)], p<.001. Web-based treatment produced a greater reduction in quantity of use in last 30 days from baseline to 3-month follow up [21.7(19.9) – 13.1(29.7)] compared to waiting list [21.8(19.90) – 16.5(26.8)], p=.003.
Mason et al., 2018	Peer-network counselling text treatment (n = 51), 4-week Assessment-only control (n= 50), 4-week	Peer-network text intervention reduced past-30 day use from baseline to end of treatment, [24.2(6.1) – 20.8(8.5)] which was not significantly different to assessment-control [23.9(6.2) – 20.2(8.6)]. Peer-network text reduced prevalence of cannabis-related relationship problems from baseline to 3 month follow up (53% - 11%), a greater increase than in the assessment-control (28% - 14%), p<.05.

Table 2. Study design and primary endpoint data for pharmacological interventions for CUD

Study	Interventions	Primary endpoint(s)
Levin et al., 2011	Dronabinol 20mg (n = 79), 12-week (one-week placebo lead-in, one week titration, 6-week medication maintenance, 2-week taper dose, 2-week placebo lead out) Placebo (n= 77), 12-week Both interventions paired with a weekly coping skills psychosocial intervention	Dronabinol did not significantly influence rates of 2-week abstinence compared to placebo at the end of treatment (17.72% vs 15.58%).
Allsop et al., 2014	Nabiximols (n =27), 6-day in-patient detoxification (Day 1 = 43.2 THC + 40mg CBD, Days 2-3 = max 86.4mg THC, 80mg CBD, Day 4 = max 64.8mg THC, 60mg CBD, Day 5 = 10.8mg THC, 10mg CBD, Day 6 = 5.4mg THC, 5mg CBD) Placebo (n =24), 6-day in-patient detoxification	Nabiximols treatment produced a reduction in scores on the Cannabis Withdrawal Scale from onset of treatment to days 2-6, [2.51 (1.57) - 1.88 (1.64)], which was significantly greater than the placebo group [1.68 (0.96) - 2.22 (1.62)], p=.01. Patient retention was greater during the inpatient detoxification in the Nabiximols group (85% remained in treatment at day 6) vs the placebo group (50% remained in treatment at day 6), p=.02.

	Both interventions paired with CBT-based self-completed workbook and guided psychotherapy	
Trigo et al., 2018	Nabiximols, self-titrated: range from 11g THC + 10.2mg CBD – 34.5mg THC + 31.9mg CBD (n= 20), 12 week Placebo (n= 20), 12-week Both paired with weekly MET/CBT	Nabiximols treatment did not significantly influence cannabis use compared to placebo in 7-day point prevalence of abstinence after the medication phase (30.8% vs 42.9%).
Lintzeris et al., 2019	Nabiximols, (n = 64) 12-week; 3-day dose induction period, then maximum daily dose 86.4mg THC + 80mg CBD, doses titrated at weekly clinical interview Placebo (n= 73), 12-week Both paired with 6-week CBT counselling	Nabiximols treatment produced a reduction infrequency of cannabis use during treatment (mean 35/84 days), compared to placebo (mean 53.1/84 days), p=.02.
D'Souza et al., 2019	PF-04457845, 4mg once daily (n=46), 5-8 days inpatient, 20-23 day outpatient phase Placebo (n=24), 5-8 days inpatient, 20-23 day outpatient phase	PF-04457845 treatment produced significantly reduced cannabis withdrawal symptoms on Day 0 (6.04 vs 11, p=.048) and Day 1 (6.02 vs 11.74, p=.035) but not Day 2 (8.78 vs 9.54, p=.709), Day 3 (6.80 vs 8.74, p=.812) or Day 4 (7.65 vs 9.04, p =.979) of inpatient treatment, compared to placebo. PF-04457845 treatment reduced cannabis use (joints per day) at week 4 [0.40(0.25 – 0.62)] compared to placebo [1.27(0.82-1.97)], p<.001.

		PF-04457845 treatment significantly reduced urinary THC-COOH levels at week 4 [265.55(175.60 – 401.57)] compared to placebo [657.92(381.60-1134.30)], p=.009.
Freeman et al., 2020	200mg CBD (n=12), 4-week (group eliminated at interim analysis) 400mg CBD (n = 24), 4-week 800mg CBD (n=23), 4-week Placebo (n=23), 4-week All groups paired with 6 sessions of motivational interviewing	400g CBD decreased urinary THC:COOH at the end of treatment (posterior probability=0.9995; -94.21 ng/ml; 95% CI: -161.83, -35.56), as well as increased days abstinent (posterior probability=0.9966; +0·48 days per week; 95% CI: 0.15, 0.82), compared to placebo. 800mg CBD decreased urinary THC:COOH at the end of treatment (posterior probability=0.9965; -72.02 ng/ml; 95% CI: -135.47, -19.52), and increased days abstinent (posterior probability=0.9247; +0.27 days per week, 95% CI: -0.09, 0.64), compared to placebo.
Gray et al., 2012	N-acetylcysteine, 2400mg daily (n=58), 8-week Placebo (n=58), 8-week Both paired with twice-weekly contingency management	N-acetylcysteine increased the odds of a negative urine test for cannabis use during the treatment period compared to placebo (40.9% vs 27.2%), OR= 2.4 (1.1-5.2), p=.029.
Gray et al., 2017	N-acetylcysteine, 2400mg daily (n=153), 12-week Placebo (n=149), 12-week Both paired with twice-weekly contingency management	N-acetylcysteine treatment did not influence the odds of a negative urine test for cannabis during treatment compared to placebo (22.3% vs 22.4%), OR = 1 (0.63-1.59), p =.984.

Mason et al., 2012	Gabapentin 1200mg daily (n =25), 12-week Placebo (n =25), 12-week Both paired with weekly abstinence-oriented counselling	Gabapentin treatment significantly reduced grams of cannabis per week at the end of treatment compared to placebo (p=.004) Gabapentin treatment was significantly reduced in urinary THC-COOH at the end of treatment compared to placebo (p=.001)

Table 3. Study design and primary endpoint data for targeted interventions for comorbid CUD and psychosis

Study	Interventions	Primary endpoint(s)
Hjorthoj et al 2013	CapOpus (motivational interviewing and CBT tailored for cannabis-related problems + treatment as usual (n =52), 6-month Treatment as usual (n =51), 6-month	CapOpus treatment did not influence the ratio of days with cannabis use compared to treatment as usual [0.76, (95% CI 0.38–1.50] p=0.42.
Rabin et al 2018	Contingency management in schizophrenia patients (n = 19) Contingency management in non-psychiatric controls (n =20) Both paired with weekly supportive therapy including motivational interviewing, psychoeducation and coping skills	Contingency management produced 68.4% self-reported abstinence during treatment in schizophrenia patients, compared to 95% in the control patients. Contingency management produced 47.3% urinary-confirmed abstinent in schizophrenia patients, compared to 40% of control patients.
Sheridan-Rains et al., 2019	Contingency management + 6 session psychoeducation (n = 278), 12-week Psychoeducation (n =273), 12-week	Contingency management treatment was not associated with reduced time to admission to an acute psychiatric service compared to the psychoeducation control [Hazard ratio = 1.03 (0.76, 1.40)].
Smeerdijk et al 2015	Family Motivational Intervention (Parents n =53; Patients n =37), 6-month Routine family support (Parents n =44; Patients n =38), 6 month	Family motivational intervention reduced mean days of cannabis use from baseline to 3-month follow-up [56.12(28.55) – 15.24(25.45)], compared to routine family support [52.88 (32.02) - 40.05 (33.14)], p<.01.

Schnell et al., 2014	Clozapine average daily dose 225mg (n =14), 12-month Ziprasidone average daily dose 200mg (n =16), 12-month Both groups offered integrated treatments including pharmacotherapy, clinical management, psychoeducation, CBT	Clozapine did not reduce frequency of cannabis use (joints per month) compared to Ziprasidone, p=.128.
Machielsen et al 2012	Cross-sectional analysis of cohort study data Risperidone, mean dose 3.45mg (n= 48) Olanzapine, mean dose 13.78mg (n= 52) Clozapine, mean dose 350mg (n= 23)	OCDUS (Obsessive Compulsive Drug Use Scale) total score was higher in patients who had been prescribed risperidone (1.83) compared to Olanzapine (1.54) or Clozapine (1.33), p=.005. Scores on the "Craving" subscale of the OCDUS were higher in patients who had been prescribed risperidone (1.83), compared to Olanzapine (1.50) or Clozapine (1.17), p=.007.

Table 4. Study design and primary endpoint data for targeted interventions for comorbid CUD and anxiety or depression

Study	Interventions	Primary endpoint(s)
Buckner and Carroll, 2010	MET + CBT, 9 session (n =156), 12 week MET, 2 sessions (n =146), 1- and 5- week post-randomisation Delayed treatment control (n =148), 4-month	MET + CBT treatment produced significantly lower STAI anxiety scores compared to MET at 4-months [30.80(0.90) vs 33.59(0.96)], and 9-months [30.64(0.86) vs 34.36(0.92)] p<.05.
Buckner et al., 2019	ICART (MET-CBT tailored for cannabis and anxiety), 12 session (n =27), 12-week MET-CBT (tailored for reduction of anxiety), 9 session (n =28), 12-week	ICART treatment produced greater completion of 9-sessions of treatment* (59.3%) than MET-CBT (25%), p=.010. *endpoint chosen as the greatest number of weeks that could be compared due to MET-CBT treatment having fewer sessions than ICART. Negative urinary tests for cannabis were not significantly different between conditions during treatment (11.1% vs 3.6%, p= .282) or at Week 12 (12% vs 0%, p =.059).
Kay-Lambkin et al., 2009	9 session tailored therapist-delivered CBT(n=35), 3-month 9 session tailored computer-delivered CBT (n=32), 3-month Brief intervention only (n=30), one session	Therapist-delivered CBT produced improvements in depression from baseline to 12-month [34.9(9.7) – 20.35(14.49)] compared to brief intervention [32.86(9.59) – 24.76(12.55)]. Computer-delivered CBT also produced improvements in depression from baseline to 12 -month [28.57(9.89) – 13.65(9.55)] compared to the brief intervention. Therapist-delivered CBT produced a reduction in cannabis use occasions per day from baseline to 12 months [15.03(13.87) – 5.72(6.22)] compared to brief intervention [9.22(8.57) – 8.61(10.16)], p <.001. Computer delivered CBT also produced a reduction in cannabis use occasions per day from baseline to 12 months [11.94(9.14) – 3.34(5.52)], compared to brief intervention.

Cornelius et al., 2010	Fluoxetine, starting dose 10mg daily, increased to 20mg target dose at week 3 (n=34), 12-week Placebo (n=36), 12-week Paired with nine session of CBT + MET	Fluoxetine treatment reduced BDI total scores from baseline to end of treatment [18.06(8.80) – 7.79(7.98)], a non-significant decrease compared to placebo [16.64(9.85) – 7.31(8.29)], p=.803. Fluoxetine treatment decreased days of cannabis used per week from baseline to end of treatment [4.61(2.18) = 3.88(2.60)] a non-significant reduction compared to placebo [4.35(1.93) – 3.10(2.27)], p=.182. Fluoxetine treatment reduced DSM-IV-TR cannabis dependence from baseline to end of treatment [4.88(1.63) – 3.29(2.11)] a non-significant reduction compared to placebo [5.19(1.35) – 3.14(1.74), p =.738.
Levin et al., 2013	Venlafaxine, 225mg daily, max 37mg day after week 4, (n=51), 12-week Placebo (n=52), 12-week Paired with weekly CBT and relapse prevention treatment	Venlafaxine treatment resulted in 11.8% of the sample achieving 2 consecutive urine-confirmed abstinent weeks, significantly less than achieved in the placebo group (36.5%), p<.001. Venlafaxine treatment resulted in 62.7% achieving a 50% reduction of Hamilton depression score at end of study, a non-significant difference from the placebo group (69.2%), p=.51. Venlafaxine treatment resulted in 51% achieving a score <8 on the Hamilton Depression Rating Scale at the end of treatment, a non-significant difference from the placebo group (57.7%), p=.33.